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REMARKS/ARGUMENTS

The claims remain as 1 to 8 and 10 to 14.

Examiner Stockton is thanked for the opportunity to discuss the application on February 24, 2004. The substance of Applicants' presentation appears below.

BASIS FOR AMENDMENTS

Claim 1 is amended to correct a typographic error in regard to R^1.

Claim 10 is amended to insert a list of treatable ailments at the appropriate location in the claims. Basis appears in original Claim 10 as well as in the paragraph bridging pages 88 and 89 of the specification.

Claim 10 is also amended to change "and/or" to "or", as suggested in the Official Action.

Claim 11 is amended to correct the nomenclature in regard to alternative (11) for R^6. The ester linkage involved is more accurately identified by "alkoxycarbonyl" than by the terminology now in the claim. In this connection please see the remarks at page 17 of the Preliminary Amendment in regard to R^6.

THE CLAIM REJECTIONS

Reconsideration and withdrawal of the rejection of Claim 10 under 35 U.S.C. § 112, first paragraph, is requested.

The claims are here amended to recite the disclosed itemization of diseases which are treatable with a compound having hypoglycemic activity. The subject compounds have such activity, as demonstrated in the pharmaceutical data obtained by the procedure appearing on pages 19-21 of the specification. Guidance for their use appears in the paragraph at line 5 on page 21. The group of the diseases appears in allowed claim 8.

The medical procedures for treatment of patients with hypoglycemically active pharmaceutical compounds are well known and long established. It would therefore appear that, in the absence of specific information to the contrary, Applicants' assertions concerning the applicability of their compounds, certainly as now claimed, should be accepted. It would appear that the In re Wands 8 USPQ2d 1400 (1988) criteria are adequately satisfied.

Reconsideration and withdrawal of the rejection of Claims 2, 3, 5 and 10 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention are requested.

The Official Action indicates that Claim 2 does not further limit Claim 1 and that compounds 30 and 31 in the claim 5 are not embraced by Claim 1.

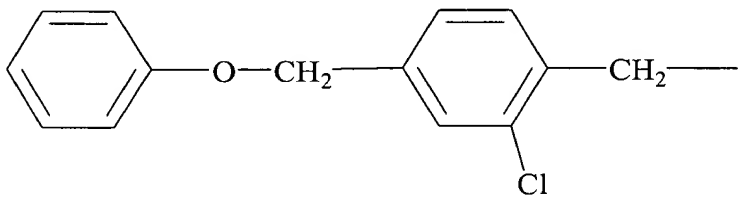
Applicants respectfully maintain that Claim 2 does in fact further limit Claim 1 in regards to definition (10) under variable R^6.

The above may be established by considering the compound 30 in Claim 5 in regard to the R^1 definition, emphasized in the Official Action.

R^1-A- appearing in formula (I) in Claim 1 is intended to include the grouping

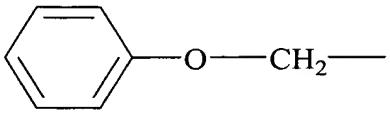
-1-(2-chloro-4-(phenoxymethyl)benzyl)

appearing in compound 30. This can be presented as:



(F)

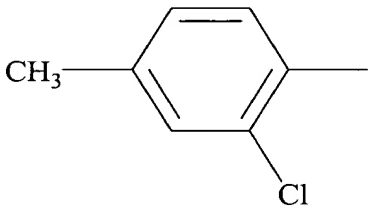
This is clearly included by the formula (IA) in Claim 2 where the "CH_2" group appears as the kink in the line linking the chlorine-substituted benzene ring to the 1-N of the imidazole ring and R^6 is defined as (10) lower alkyl optionally substituted by aryloxy. The

last reads on the  grouping recited for the compound 30 of Claim 5.

The point at issue is whether the compound 30 structure discussed above and the Claim 2 structure for the group joined to the 1-N of the imidazole ring are within the scope of the structure for the corresponding substituents as depicted in formula (I) of Claim 1, namely the grouping -A-R^1.

In Claim 1, "A" is defined as "lower alkylene". This is readable on the right hand -CH_2- group of formula (F) above.

In Claim 1, R^1 is preliminarily defined as "an aryl which is substituted by halogen at the ortho position relative to the point of attachment of R^1 to A", and the claim further states that "aryl is defined as unsubstituted aryl or alkyl substituted aryl." Accordingly, the structure (G) drawn below is within the scope of that portion of the definition of R^1.

 (G)

Such a structure, when not in radical form, could be named as *m*-chlorotoluene, compared in the attached page 386 of Morrison and Boyd 3rd Edition noting *o*- and *p*-substitution. It is thus an aryl substituted by chlorine, even though it bears the methyl group. The toluene radical is a recognized aryl group since toluene is a recognized aromatic compound.

Claim 1 finally requires, in defining R^1, that it be substituted by the specified substituent(s), including (10) aryloxy. This leads to structure (F) above when the aryloxy substituent is phenoxy and is placed on the CH_3 group of the depicted o-chlorotoluene radical, i.e., in the α-position. Substitution of an aryl radical can be on a side chain since the

term "aryl radical" includes those with a free valence on the side chain, IUPAC Nomenclature of Organic Chemistry (1979), pages 19 and 20, Rules 13.3 and 13.5, copy attached. Hence such a substitution in the α-position of the chlorotoluene radical is substitution of an aryl radical.

It follows from the above that Claim 2 further limits Claim 1 and that compounds 30 and 31 (which involve the same issues) are embraced by Claim 1.

The Official Action at page 7 states, in summarizing Applicants' previous arguments on the point, that

> It could not be found in any of the definitions that the "alkyl" group is optionally substituted or that the "aryl" group (represented by R^1) can optionally be substituted with an "aryloxyalkyl" group. Therefore, the rejection is deemed proper and is maintained.

In comment thereon, Applicants point out that the claims do not employ terminology which literally specifies that an "aryl" group or an "alkyl group" be substituted by an "aryloxyalkyl". It is not necessary. If one grants that "toluene" is an aromatic compound, one has a choice of naming "toluene" substituted by say "phenoxy" on the methyl group as "phenoxymethyl benzene", which is the approach taken in naming compounds (30) and (31) in Claim 5, or as α-phenoxytoluene, which is in effect the approach taken by Applicants in Claim 1. In Claim 2 and in Claim 5, the "aryl" of Claim 1 is specialized to "phenyl." In this connection please note the alternative names for benzyl chloride appearing on page 114 of Kirk-Othmer, The Encyclopedia of Chemical Technology, 4th Ed., vol. 6, page 114, copy attached. As previously noted, basis for the definition of aryl appearing in claim 1 is to be found at page 6, line 34 to page 7, line 6 and pages 817 and 820 of the Morrison and Boyd text.

Claim 3 would appear to be free of the stated criticism.

Reconsideration of the stated holdings with respect to Claims 2, 3 and 5 are therefore requested.

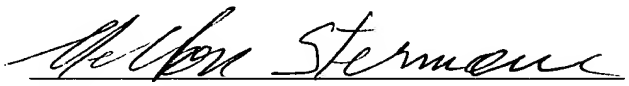
With respect to Claim 10, the suggested change is made.

Entry of the herewith submitted amendment is requested as raising no new issues and as simplifying the issues.

Favorable reconsideration is solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



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Sections A, B, C, D, E, F and H

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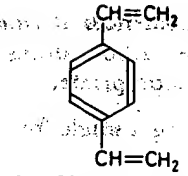
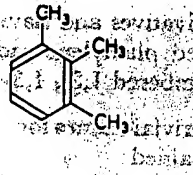
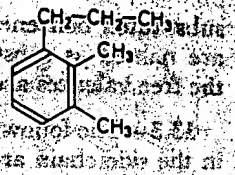


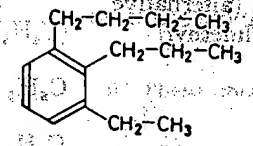
1,4-Divinylbenzene
or *p*-Divinylbenzene
not *p*-Vinylstyrene



1,2,3-Trimethylbenzene
not Methylxylene
not Dimethyltoluene



1,2-Dimethyl-
3-propylbenzene
or 3-Propyl-*o*-xylene



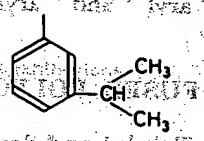
1-Butyl-3-ethyl-2-propylbenzene

12.4—The generic name of monocyclic and polycyclic aromatic hydrocarbons is "arene".

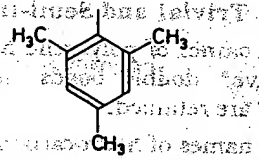
Rule A-13. Substituted Aromatic Radicals

13.1—Univalent radicals derived from monocyclic substituted aromatic hydrocarbons and having the free valence at a ring atom are given the names listed below. Such radicals not listed below are named as substituted phenyl radicals. The carbon atom having the free valence is numbered as 1.

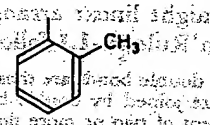
Phenyl C_6H_5—



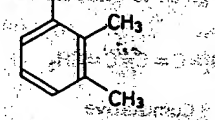
Cumenyl (*m*- shown)



Mesityl



Tolyl (*o*- shown)



Xylyl (2,3- shown)

13.2—Since the name phenylene (*o*-, *m*- or *p*-) is retained for the radical —C_6H_4— (exception to Rule A-11.6), bivalent radicals formed from

substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. The carbon atoms having the free valences are numbered 1,2-, 1,3- or 1,4- as appropriate.

13.3—The following trivial names for radicals having a single free valence in the side chain are retained:

Benzyl	$C_6H_5—\overset{\alpha}{C}H_2—$
Benzhydryl (alternative to Diphenylmethyl)	$(C_6H_5)_2\overset{\alpha}{C}H—$
Cinnamyl	$C_6H_5—\overset{\gamma}{C}H=\overset{\beta}{C}H—\overset{\alpha}{C}H_2—$
Phenethyl	$C_6H_5—\overset{\beta}{C}H_2—\overset{\alpha}{C}H_2—$
Styryl	$C_6H_5—\overset{\beta}{C}H=\overset{\alpha}{C}H—$
Trityl	$(C_6H_5)_3C—$

13.4—Multivalent radicals of aromatic hydrocarbons with the free valences in the side chain are named in accordance with Rule A–4.

Examples:

Benzylidyne $C_6H_5—\overset{\alpha}{C}\equiv$

Cinnamylidene $C_6H_5—\overset{\gamma}{C}H=\overset{\beta}{C}H—\overset{\alpha}{C}H=$

13.5—The generic names of univalent and bivalent aromatic hydrocarbon radicals are " aryl " and " arylene ", respectively.

FUSED POLYCYCLIC HYDROCARBONS

Rule A–21. Trivial and Semi-trivial names

21.1—The names of polycyclic hydrocarbons with maximum number of non-cumulative* double bonds end in " -ene ". The names listed on pp. 21 and 22 are retained.

21.2—The names of hydrocarbons containing five or more fused benzene rings in a straight linear arrangement are formed from a numerical prefix as specified in Rule A–1.1 followed by " -acene ". [Examples on p. 22]

* Cumulative double bonds are those present in a chain in which at least three contiguous carbon atoms are joined by double bonds; non-cumulative double bonds comprise every other arrangement of two or more double bonds in a single structure. The generic name " cumulene " is given to compounds containing three or more cumulative double bonds.

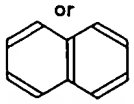
Examples:

$CH_2=C=C=C=CH_2$

Cumulative

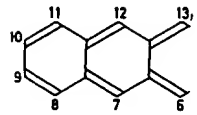
$CH_3-CH=CH-CH=CH-CH=CH_2$

or



Non-cumulative

Examples (to R



Pentac

The following li
are retained (see R

(1) Pentalene

(2) Indene

(3) Naphthalene

(4) Azulene 6

(5) Heptalene 8

(6) Biphenylene 7 6

(7) *as*-Indacene 7 6

(8) *s*-Indacene 6 5

(9) Acenaphthylene

(10) Fluorene 7 6

(11) Phenalene

Third Edition

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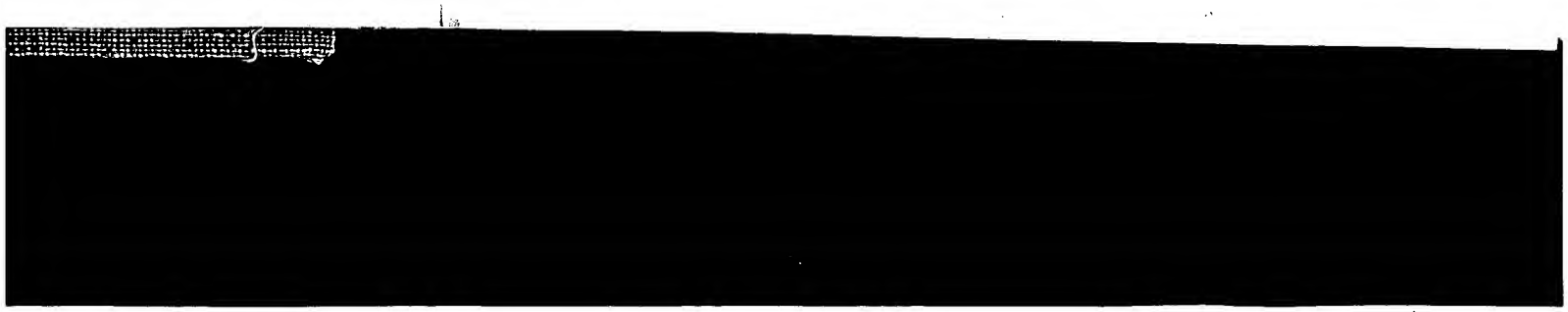


12.12 Halogenation of alkylbenzenes: ring *vs.* side chain

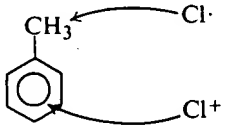
Alkylbenzenes clearly offer two main areas to attack by halogens: the ring and the side chain. We can control the position of attack simply by choosing the proper reaction conditions.

Halogenation of alkanes requires conditions under which halogen atoms are formed, that is, high temperature or light. Halogenation of benzene, on the other hand, involves transfer of positive halogen, which is promoted by acid catalysts like ferric chloride.

$$CH_4 + Cl_2 \xrightarrow{\text{heat or light}} CH_3Cl + HCl$$

$$C_6H_6 + Cl_2 \xrightarrow{FeCl_3,\ \text{cold}} C_6H_5Cl + HCl$$

We might expect, then, that the position of attack in, say, toluene would be governed by which attacking particle is involved, and therefore by the conditions employed. This is so: if chlorine is bubbled into boiling toluene that is exposed to

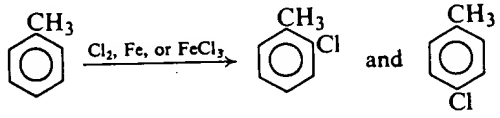


Atom: *attacks side chain*

Ion: *attacks ring*

ultraviolet light, substitution occurs almost exclusively in the side chain; in the absence of light and in the presence of ferric chloride, substitution occurs mostly in the ring. (Compare the foregoing with the problem of substitution *vs.* addition in the halogenation of alkenes (Sec. 6.21), where atoms bring about substitution and ions—or, more accurately, molecules that can transfer ions—bring about addition.)

Like nitration and sulfonation, ring halogenation yields chiefly the *o*- and

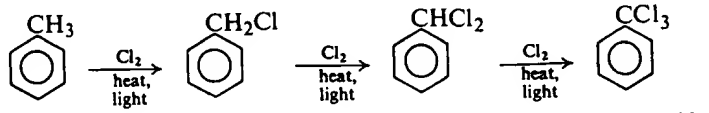


Toluene *o*-Chlorotoluene *58%* *p*-Chlorotoluene *42%*

p-isomers. Similar results are obtained with other alkylbenzenes, and with bromine as well as chlorine.

Side-chain halogenation, like halogenation of alkanes, may yield polyhalogenated products; even when reaction is limited to monohalogenation, it may yield a mixture of isomers.

Side-chain chlorination of toluene can yield successively the mono-, di-, and trichloro compounds. These are known as *benzyl chloride*, *benzal chloride*, and



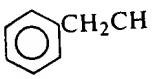
Toluene Benzyl chloride Benzal chloride Benzotrichloride

benzotrichloride; such compou
alcohols, aldehydes, and acids

12.13 Side-chain halogenat

Chlorination and bromi
orientation and reactivity in c
tion, and then at chlorination

An alkylbenzene with a s
than one position for attack,
a mixture of isomers. Bromina
yield two products: 1-bromo-



Ethylbenzene

a probability factor that fa
found is 1-bromo-1-phenyle
to the carbon next to the a

Hydrogen atoms attach
benzylic hydrogens.

The relative ease with
only by orientation of bro
parison of reactivities of
1.22) show, for example, t
reactive toward bromine a
,100 million times as react

Examination of react
by other free radicals as v
gens are extremely easy t
now expand the reactivity

Ease of abstraction of hydrogen atoms	allyl benz

Side-chain halogenat

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FOURTH EDITION

VOLUME 6

CHLOROCARBONS AND CHLOROHYDROCARBONS—C_2
TO
COMBUSTION TECHNOLOGY

1993

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to benzaldehyde; benzotrichloride is converted to benzoyl chloride. Benzyl chloride is also hydrolyzed to benzyl alcohol, which is used in the photographic industry, in perfumes (as esters), and in peptide synthesis by conversion to benzyl chloroformate [*501-53-1*] (see BENZYL ALCOHOL AND β-PHENETHYL ALCOHOL; CARBONIC AND CARBONOCHLORIDIC ESTERS).

Several related compounds, primarily ring-chlorinated derivatives, are also commercially significant. *p*-Chlorobenzotrichloride is converted to *p*-chlorobenzotrifluoride, an important intermediate in the manufacture of dinitroaniline herbicides.

Physical Properties

Benzyl chloride [(chloromethyl)benzene, α-chlorotoluene], $C_6H_5CH_2Cl$, is a colorless liquid with a very pungent odor. Its vapors are irritating to the eyes and mucous membranes, and it is classified as a powerful lacrimator. The physical properties of pure benzyl chloride are given in Table 2 (2–7). Benzyl chloride is insoluble in cold water, but decomposes slowly in hot water to benzyl alcohol. It is miscible in all proportions at room temperature with most organic solvents. The flash point of benzyl chloride is 67°C (closed cup); 74°C (open cup); autoignition temperature is 585°C; lower flammability limit: 1.1% by volume in air. Its volume coefficient of expansion is 9.72×10^{-4}.

Benzal chloride [(dichloromethyl)benzene, α,α-dichlorotoluene, benzylidene chloride], $C_6H_5CHCl_2$, is a colorless liquid with a pungent, aromatic odor. Benzal chloride is insoluble in water at room temperature but is miscible with most organic solvents.

Benzotrichloride [(trichloromethyl)benzene, α,α,α-trichlorotoluene, phenylchloroform], $C_6H_5CCl_3$, is a colorless, oily liquid with a pungent odor. It is soluble in most organic solvents, but it reacts with water and alcohol. For benzotrichloride the flash point is 127°C (Cleveland open cup) and the autoignition temperature is 211°C (8).

Binary azeotropic systems are reported for all three derivatives (9). The solubilities of benzyl chloride, benzal chloride, and benzotrichloride in water have been calculated by a method devised for compounds with significant hydrolysis rates (10).

Chemical Properties

The reactions of benzyl chloride, benzal chloride, and benzotrichloride may be divided into two classes: (*1*) reactions of the side chain containing the halogen; and (*2*) reactions of the aromatic ring.

Reactions of the Side Chain. Benzyl chloride is hydrolyzed slowly by boiling water and more rapidly at elevated temperature and pressure in the presence of alkalies (11). Reaction with aqueous sodium cyanide, preferably in the presence of a quaternary ammonium chloride, produces phenylacetonitrile [*140-29-4*] in high yield (12). The presence of a lower molecular-weight alcohol gives faster rates and higher yields. In the presence of suitable catalysts benzyl chloride reacts with

Table 2. Physica

Property
mol wt
freezing point, °C
boiling point, °C
density, kg/m^3
refractive index,
surface tension, mN/m(= dyn/c
dipole moment[a],
diffusion of vapo
cm^2/s
vapor density(ai
heat of combusti
specific heat at 2
J/kg·K)[b]
heat of vaporizat
vapor pressure, [c]
0.13
0.67
1.33
5.33
8.00
13.3
26.7
53.3

[a]In dilute benzene
[b]To convert J to ca
[c]At constant volun
[d]At constant press
[e]At 25°C.
[f]At 72°C.
[g]At 80°C.
[h]To convert kPa t

carbon monoxi
catalyst syste
phenylpyruvic
benzyl chlorid
sodium alkoxi
transfer catal
The ben
amines has be
benzylamines
the reaction o

alcohol is used in a wide spectrum of applications including pharmaceuticals and perfumes, as a solvent, and as a textile dye assistant.

Derivatives

Ring-Substituted Derivatives. The ring-chlorinated derivatives of benzyl chloride, benzal chloride, and benzotrichloride are produced by the direct side-chain chlorination of the corresponding chlorinated toluenes or by one of several indirect routes if the required chlorotoluene is not readily available. Physical constants of the main ring-chlorinated derivatives of benzyl chloride, benzal chloride, and benzotrichloride are given in Table 4.

The 2- and 4-monochloro and 2,4- and 3,4-dichlorobenzyl chloride, benzal chloride, and benzotrichlorides are manufactured by side-chain chlorination of the appropriate chlorotoluene. *p*-Chlorobenzotrichloride (1-chloro-4-trichloromethylbenzene) can be prepared by peroxide-catalyzed chlorination of *p*-toluenesulfonyl chloride or di-*p*-toluylsulfone (71). 2,4-Dichlorobenzotrichloride (1,3-dichloro-4-trichloromethylbenzene) is obtained by the chlorination of 2-chloro-4-chlorosulfonyltoluene (72).

3,4-Dichlorobenzyl chloride (1,2-dichloro-4-chloromethylbenzene) containing some 2,3-dichlorobenzyl chloride is produced by the chloromethylation of *o*-dichlorobenzene in oleum solution (73). Chlorination of 2-chloro-6-nitrotoluene at 160–185°C gives a mixture of 2,6-disubstituted benzal chloride and 2,6-dichlorobenzyl chloride (74).

The ring-chlorinated benzyl chlorides are used in the preparation of quaternary ammonium salts and as intermediates for pharmaceuticals and pesticides. *p*-Chlorobenzyl chloride is an intermediate in the manufacture of the rice herbicide, Saturn ((*S*-4-chlorobenzyl)-*N*,*N*-diethylthiolcarbamate [*28249-77-6*]) (75). The *o*- and *p*-chlorobenzal chlorides (1-chloro-2-and 4-dichloromethylbenzenes) are starting materials for the manufacture of *o*- and *p*-chlorobenzaldehydes.

The *o*- and *p*-monochloro- and 2,4- and 3,4-dichlorobenzotrichlorides are intermediates in the manufacture of the corresponding chlorinated benzoic acids and benzoyl chlorides. Fluorination of the chlorinated benzotrichlorides produces the chlorinated benzotrifluorides, intermediates in the manufacture of dinitroaniline and diphenyl ether herbicides (76).

2,6-Dichlorobenzal chloride is used in the manufacture of 2,6-dichlorobenzaldehyde and 2,6-dichlorobenzonitrile (77). With the exception of certain products used in the manufacture of herbicides, the volume of individual compounds produced is small, amounting to no more than several hundred tons annually for any individual compound.

Side-Chain Chlorinated Xylene Derivatives. Only a few of the nine side-chain chlorinated derivatives of each of the xylenes are available from direct chlorination. All three of the monochlorinated compounds, α-chloro-*o*-xylene (1-(chloromethyl)-2-methylbenzene [*552-45-4*]), α-chloro-*m*-xylene (1-(chloromethyl)-3-methylbenzene [*620-19-9*]), α-chloro-*p*-xylene (1-(chloromethyl)-4-methylbenzene [*104-82-5*]) are obtained in high yield from partial chlorination of the xylenes. 1,3-Bis(chloromethyl)benzene [*626-16-4*] can be isolated in moderate yield from chlorination mixtures (78,79).

Table 4. Physical Constants of the Main Ring-Chlorinated Derivatives of Benzyl Chloride, Benzal Chloride, and Benzotrichloride